REMARKS

Applicant respectfully request reconsideration of the present application in view of the foregoing amendments and in view of the reasons that follow.

I. Status of the claims

Claim 1 is amended to incorporate therein the subject matter of previously pending claim 9, which depended from claim 1. Claim 9 is amended to replace "30%" with "35%," and is supported by page 3 of the specification.

Claims 16 and 17 are new. Claim 16 is supported by Table 1 of the specification, which shows that about 11% of the sugar chains contain a bisecting GlcNAc. Claim 17 is supported by the specification at page 2, line 27 to page 3, line 7, Example 7 (pages 16, line 30 to page 17, line 17) and Example 12 (page 23, lines 12-26).

Claims 6-8 were previously cancelled. Method claims 10-12 are withdrawn pursuant to Applicant's election of February 6, 2008, pending allowance of the product claims under examination. Because claim 17 recites a method, it is also withdrawn.

No new matter is added by the foregoing amendments. Also, no new search is required because the subject matter of the pending claims under examination has already been searched and examined. The foregoing amendments are made solely to advance prosecution and without disclaimer of any subject matter removed by amendment.

Upon entry of the foregoing amendment, claims 1-5 and 9-17 are pending, and claims 1-5, 9 and 13-16 are under examination.

II. Rejection under 35 U.S.C. § 102(e)

A. The rejection

In the response of October 20, 2009, Applicant noted that the inherency argument must fail because the glycosylation pattern is not *necessarily* present, citing not only to variability caused by growth conditions, but also to the fact that Kanda examined and did not identify the claimed glycosylation pattern. The Examiner has not found these arguments persuasive, and so the rejection of claims 1-5, 9 and claims 13-15 as allegedly anticipated by Patent Application Publication No. US 2003/0115614 A1, to Kanda *et al.* ("Kanda") is maintained at pages 3-6 of the Office Action. Applicant respectfully traverse the rejection for reasons of record, and further in view of the following supplemental comments. The response will address individual aspects of the rejection in turn.

B. The anti-HM1.24 antibody

Page 4 of the Action states that "Applicant has not disputed that Kanda et al. teach anti-HMl.24 antibody but argues that Kanda's method of producing antibody would not have inherently yielded the N-glycoside-linked sugar as claimed." Applicant does ***not*** agree that Kanda's disclosure of an antibody against HM1.24 is legally sufficient to constitute anticipation under 35 U.S.C. § 102 because that antibody is merely one among a laundry list, and the disclosure is made without information attesting to a reduction to practice or reasonable expectation of success. Applicant had not previously disputed this point because it is secondary to the main issue of glycosylation, discussed below. Because Kanda's own disclosure clearly indicates that production of antibodies in YB2/0 cells does *not* result in the claimed glycosylation profiles, it is unnecessary to further argue the issue of HM1.24 antibodies.

C. Kanda *demonstrates* that the claimed glycosylation is not produced

As already mentioned in the previous reply, Kanda does not disclose a sugar chain with a bisecting GlcNAc containing no α1,6 core fucose. Because Kanda does not demonstrate the presence of the claimed glycosylation patterns, the Examiner asserts that such glycosylation patterns are *inherently* present as a matter of logic and reason. For example:

> The Examiner acknowledges that cell culture conditions would probably contribute to the percentage of the content of N-glycan. However, the genetic contents of the host cells (e.g. genes encoding glycosylation enzymes) would determine the structure of the N-glycan on the glycoproteins being produced. Here, contrary to applicant's assertion that the host cells, e.g. engineered YB2/0, *would not inherently produce* the N-glycan structure being claimed, it is noted that the instant sugar chain altered anti-HMl.24 antibody is produced in YB2/0 because YB2/0 has low fucose transferring activity.
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> . . .
>
> *Thus, it is reasonable to conclude that the prior art host cells would produce an antibody without fucose.*
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> . . . .
>
> *Since the prior art antibody is produced in host cells without fucose transferase, it is reasonable to conclude the antibody would not have fucose, thus would meet the claimed fucose free sugar chain of 30% or more.*

Office Action at page 4-6, emphasis added. That is, because YB2/0 cells have no fucose transferase activity, the Examiner *reasons* that production of antibodies in YB2/0 *must* lack fucose and result in the instantly claimed antibodies. The Examiner then places the burden on Applicant to prove that Kanda does not produce the claimed antibodies, stating at page 5 that "it is applicant's burden to show that the reference antibody produced in engineered host cells including YB2/0 with fucose transferase knockout does not have the sugar chain structure as recited in the claims."

The Rejection then asserts that "*Applicant has not submitted objective evidence* to show that engineered host cells taught by Kanda et al. (e.g. YB2/0 with fucose transferase knock-out) would not produce an antibody having the N-glycan as claimed." Office Action at page 5, emphasis added. Because such evidence is missing, the Examiner reasons that the rejection must be maintained.

The Rejection is incorrect based on the facts *already of record.*

The YB2/0 cell line has a defect in fucose transferase (FUT8) and so, as acknowleged by the Rejection, has low or no fucose transferase activity. The Rejection pointed out that the YB2/0 was chosen in the present application because it has low fucose transferring activity. Based on this the Rejection concluded that the prior art host cell would produce antibodies without fucose. This is clearly contradicted by Table 1 on page 41 of Kanda, which shows that 47% of sugar chains from YB2/0 cells are fucosylated. *See also* Table 2, showing the relative ratio of fucose and other monosaccharide species on antibodies from different sources.

Even more relevant to the present issue, Kanda clearly describes *what* antibodies are produced. Example 11 of Kanda describes an experiment to examine the effect of FUT8 on antibody glycosylation. To this end, FUT8 was cloned into the pAGE249 vector. One clone, "mfFUT8-6," particularly over-expressed FUT8. Kanda then expressed antibody in a cell with mfFUT8-6 (over-expressing FUT8), and one with pAGE249 (the cloning vector) as a negative control. The isolated sugar chains produced by both cell lines were analyzed as described in Kanda:

> [0884]FIG. 30 shows elution patterns obtained by carrying out reverse phase HPLC analysis of each of PA-treated sugar chains prepared from antibodies produced by mfFUT8-6 and pAGE249-introduced cell lines. FIGS. 30A and 30B show elution patterns of mfFUT8-6 and pAGE249, respectively.
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> . . .
>
> [0885] Peaks (i) to (ix) shown in FIG. 30 and FIG. 31 show the following structures.

In paragraph [885] the structures of the found sugar chains are shown. Only one of them, structure (ix), has a bisecting GlcNAc and has an α 1,6 fucose. In other words, the only sugar chain with a bisecting GlcNAc is fucosylated.

Therefore Kanda examined the glycosylation profile of antibodies produced from YB2/0 cells with a defect in FUT8, and *did not find the claimed glycosylation patterns.* Accordingly, Applicant *has met its burden and submitted objective evidence* to show that

engineered host cells taught by Kanda (e.g., YB2/0 with fucose transferase knock-out) would not produce an antibody having the N-glycan as claimed. Against the Rejection's rationalizations of what "is *reasonable* to conclude," (Office Action at page 5) the Rejection's own reference *directly rebuts* the Rejection, showing that YB2/0 cells do not produce the claimed glycosylation patterns.

Accordingly, the present rejection based on Kanda must fail because Kanda demonstrates that the claimed species was absent as "a question of fact," under the standards of *In re Napier*, 55 F.3d 610, 613, 34 USPQ2d 1782, 1784 (Fed. Cir. 1995). *See also In re Grasselli*, 713 F.2d 731, 739, 218 USPQ 769, 775 (Fed. Cir. 1983), MPEP § 2112.

D. Kanda demonstrates additional differences

Not only does Example 11 show an absence of the claimed fucose-free bisecting antibody species, but it also shows additional differences from the Applicant's specification. Structure (ix), has a bisecting GlcNAc and has an α 1,6 fucose. In Figure 30B, the elution pattern shows that the amount of sugar chain of structure (ix) is very low compared to the sugar chains without bisecting GlcNAc. By comparison, more than 10% of the sugar chains disclosed in the present application have bisecting GlcNAc. Therefore, not only is claim 16 free from Kanda but, in general, the sugar chains disclosed in Kanda differ from those identified in Applicant's specification. This confirms Applicant's position that the identity of the host cell is important in the production of the sugar chain, and it has been documented with the articles cited in the previous reply (i.e. Jenkins et al., Enzyme Mircob. Technol., 1994 16: 354-64) that different external factors, i.e. culturing condition, also have an influence. All sugar chains of the antibodies were analyzed in Kanda, and the claimed structure was not found. Therefore, the structure was not there, and is thus not inherently disclosed.

The Rejection pointed out that the YB2/0 was chosen in the present application because it has low fucose transferring activity. Based on this, the Rejection concluded that the prior art host cell would produce antibodies without fucose. However, Kanda also chose the YB2/0 for the same reason and showed an effect of the amount of fucosylation of the

sugar chains. Nonetheless, Kanda failed to produce the specific structure. This clearly shows that external factors influence the sugar chain formation. If the host cell and the expression levels of FUT8 would be the only determining factors, the claimed structure would have been found in the analysis of the sugar chains produced with the control cell line.

E. Summary

The anticipation rejection over Kanda relies on a theory of inherency based on "reasonable" predictions, but this rejection is specifically and unambiguously rebutted by Kanda itself. When Kanda examined the glycosylation pattern on antibody expressed from YB2/0 cells, without *trans* FUT8, the only antibody with bisecting GlcNAc also possessed an α 1,6 fucose, and therefore failed to meet the limitations of the claims. Moreover, because the glycosylation patterns identified by Kanda shows numerous additional differences from those of the present specification, Kanda undermines the assumption that expression from YB2/0 cells inherently results in the claimed pattern of glycosylation.

III. Obviousness

A. The references do not provide all elements

At pages 6-8 of the Office Action, claims 1-5, 9 and 13-15 are newly rejected under 35 U.S.C. § 103 over the combination of U.S. Patent No. 6,699,974 ("Ono"), and U.S. Patent No. 6,602,684 ("Umana"). Applicant respectfully traverses.

Ono discloses chimeric and humanized anti-HM1.24 antibodies showing ADCC activity but does not disclose glycosylated antibodies. Umana does not disclose glycosylated HM1.24 antibody, but more generally discloses a method for glycosylation engineering of proteins in order to improve the therapeutic properties using host cells which are engineered to overexpress N-acetylglucosaminyaltransferase (GnTIII). Umana further discloses that sugar chains with bisecting N-acetylglucosamine may or may not be fucosylated. Although Umana discloses bisecting sugar chains, it does not disclose that of all sugar chain on the antibody the relative ratio of fucose-free sugar chains is 30% or more, as presently claimed. Accordingly, the combination of Umana and Ono does not provide all elements of claim 1.

B. The rejection relies on the poorly supported or contradicted reasoning of Umana

At page 7, the Rejection states:

> Umana et al. characterized the N-glycan of said antibodies to be Manβ14GlcNAcβ1- 4GlcNAc core structure and without core fucose but have bisecting GlcNAc (e.g. see Figures 9-11). Furthermore, Umana et al. teach that antibodies produced in the engineered host cells expressing GnT III have higher accumulation of non-fucosylated bisecting sugar chain because N-linked oligosaccharides which are first modified by GnT III can no longer be biosynthetic substrates for core α1,6-fucosylaltransferase (e.g. see column 26 and Figures 9-11).
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> It would thus be obvious to one of skill in the art to produce humanized anti-HM1.24 antibody taught by Ono et al. using GnT III engineered host cells taught by Umana et al. because anti-HM1.24 antibody exhibiting ADCC function is therapeutically effective in treating B cell malignancy and antibodies produced in GnTIII engineered host cells would have altered glycan structure, which in term, exhibits enhanced ADCC function.

As an initial matter, the § 103 rejection, like the § 102 rejection, relies on appeals to theory that are not supported by the facts. For example, the reasoning that fucosylation is less in bisected oligosaccharides because "N-linked oligosaccharides which are first modified by GnT III can no longer be biosynthetic substrates for core α1,6-fucosylaltransferase (e.g. see column 26 and Figures 9-11)" is contradicted by Kanda, in which the *only* bisected antibody (i.e. modified by GnTIII) was also fucosylated; and Umana, who report numerous bisected fucosylated antibodies. If not contradicting the Rejection's argument, these references at least call into question how far the Rejection's argument can be applied beyond the narrow facts of Umana.

The specific reference in Umana to a reduction in fucosylated (m/z 1810) versus non-fucosylated (m/z 1664) antibodies concerns the bisected hybrid species on Figure 11, with the M_4GnGn^bG or M_5GnGn^b structure (structures illustrated on Figure 1). These species do not read on claims 13-15. Moreover, Umana's conclusion is based on molecular weights, but it

is unclear how Umana can distinguish the bisected M_4GnGn^bG or M_5GnGn^b structures and the *non-bisected* galactosylated bi-antennary complex with the $M_3Gn_2G_2$, whose fucosylated (m/z 1810) and non-fucosylated (m/z 1664) antibodies have the same molecular weights. As a non-bisected species, $M_3Gn_2G_2$ is not relevant to the present claims. Thus, the increase in the (m/z 1664) species does not *per se* demonstrate an increase in bisected antibodies, and Umana's conclusions should not be taken at face value.

Yet further, the glycosylation patterns identified by Applicants differ from those in Umana. For example, the dominant species identified at the lowest level of GnTIII expression is fucosylated M_3Gn_2 (m/z 1486), which constitutes almost 50% of species. By comparison, in Applicant's specification this species (equivalent to sugar chain E on Figure 1) comprise approximately 23% (Table 1). In addition, m/z1339 corresponds to unfucosylated M_3Gn_2, which are the lowest level in Figure 9 around 1%, and increases to maximal 5%. This species is equivalent to sugar chain A in Applicant's specification, and constitutes around 18% of all sugar chains (see Table 1). The general differences in glycosylation patterns call into doubt the degree to which Umana can be relied upon for the obviousness rejection. The Rejection relies on the reasoning in Umana for the obviousness rejection, yet ignores the many factual differences between Umana and Applicant's specification that show flaws in Umana's reasoning.

With the logical weaknesses in applying Umana beyond its narrow disclosure, the combination of Ono and Umana does not provide the person of ordinary skill with the *reasonable expectation of success* required for sustaining an obviousness rejection.

C. The role of fucose

As noted above, Umana does not teach or suggest that, of all sugar chains on the antibody, the relative ratio of fucose-free sugar chains is 30% or more, as presently claimed. Moreover, Umana is not concerned with the presence or absence of fucose, but only bisected oligosaccharides.

By contrast, the present invention shows that an antibody with a sugar chain which contains no α1,6-core fucose but a bisecting N-acetylglucosamine and wherein of all sugar chains on said antibody the relative ratio of all fucose-free sugar chains is 30% or more has a significantly enhanced ADCC activity (see, Figure 2 and Figure 3). Moreover, a reduction in fucosylation (Figures 2 and 3) appears to have a greater effect on enhancing ADCC than increased GnTIII expression (Figure 9). Neither Ono or Umana, or their combination, demonstrate the surprising advantages of reduced fucose to enhancing ADCC activity. The antibodies therefore exhibit a surprising result over the cited art.

D. Summary

Te combination of Ono and Umana does not render obvious the present claims because (a) the combination does not teach or suggest all elements (b) the rejection relies on a number of unfounded assumptions and an unwarranted and extrapolation of the data, and (c) the combination does not teach or suggest the surprising effect on ADCC exhibited by antibodies with fucose-free bisected oligosaccharides. Reconsideration and withdrawal are respectfully sought, therefore.

CONCLUSION

Applicant believe that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.

Examiner Dahle is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by the credit card payment instructions in EFS-Web being incorrect or absent, resulting in a rejected or incorrect credit card transaction, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petition for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

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